PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 30596P WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/01335	International filing date *(day/month/year)* 10.03.2003	Priority date *(day/month/year)* 09.03.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/30		
Applicant ONCOMAB GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the International application

Date of submission of the demand	Date of completion of this report
08.10.2003	30.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Irion, A Telephone No. +49 89 2399-8174

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/01335

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-51 as originally filed

Claims, Numbers

1-53 as originally filed

Drawings, Sheets

1/9-9/9 as originally filed

Sequence listing part of the description, pages:

1-4, filed with the letter of 13.06.2003,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 36-51

   because:

   ☒ the said international application, or the said claims Nos. 36-51 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-11,24,25,34,35,42,43,50,51
	No:	Claims	1-6,12-23,26-33,36-41,44-49,52,53
Inventive step (IS)	Yes:	Claims	7-11,24,25
	No:	Claims	1-6,12-23,26-53
Industrial applicability (IA)	Yes:	Claims	1-35, 52,53
	No:	Claims	

2. Citations and explanations

see separate sheet

Item III

III.1 With respect to claims 36-51

Claims 36-51 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(i) PCT).

Item V

V.1 Reference is made to following documents

D1: WO0183560 (UAB RESEARCH FOUNDATION) 08 November 2001 (2001-11-08)

D2: Y. HUANG ET AL.: 'Sulindac sulfide-induced apoptosis involves death receptor 5 and the caspase 8-dependent pathway in human colon and prostate cancer cells', CANCER RESEARCH 15 September 2001 (2001-09-15), vol. 61, pages 6918-6924

D3: R.D. MENG ET AL.: 'p53-independent upregulation of KILLLER/DR5 TRAIL receptor expression by glucocorticoids and interferon-gamma', EXPERIMENTAL CELL RESEARCH, 2001, vol. 262, pages 154-169

D4: WO9713844 (CAMBRIDGE ANTIBODY TECHNOLOGY LIMITED) 17 April 1997 (1997-04-17)

D5: WO0162932 (AMGEN INC) 30 August 2001 (2001-08-30)

D6: EP1106183 (GENENTECH INC) 13 June 2001 (2001-06-13)

D7: S. BRAENDLEIN ET AL.: 'Characterization of five new fully human monoclonal IgM antibodies isolated from carcinoma patients', PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, March 2002 (2002-03), vol. 43, pages 970 ABSTRACT of a oral presentation held on the 93rd Annual Meeting of the Association for Cancer Research, San Francisco, California, USA. April 06-10, 2002.

D8: S. BRAENDLEIN ET AL.: 'Human monoclonal IgM antibodies with apoptotic activity isolated from cancer patients', HUMAN ANTIBODIES, 2002, vol. 11, no. 4, pages 107-109

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 1-6, 13, 14, 17-20, 26-32, 36-39, 44-47, 52 and 53

Document D1 describes a monoclonal antibody which interacts with DR5, a receptor of TRAIL, thereby inducing an inhibition of cell proliferation and apoptosis (abstract, p. 5 l. 20-30, p. 12 l. 18-31). TRAIL receptor induced apoptosis specifically in transformed tumor cells without affecting normal cells (p. 1 l. 25-31, p. 4 l. 25-28, p. 36 l. 15-17, p. 58 l. 1-2). Such an antibody provides a potential therapeutic and diagnostic tool (p. 3 l. 7-9). Furthermore, a pharmaceutical composition comprising a pharmaceutically acceptable carrier is described (p. 5 l. 22-25, p. 30 l. 17-29). The treatment of apoptosis related diseases is described (p. 6 l. 3-5), i.e. malignancies such as lung cancer, colon cancer, ovarian cancer, and breast cancer (p. 29 l. 27-28, p. 35 l. 6-11, Example 15 on p. 68 et seq.). Furthermore, a process for inhibiting cell proliferation using said antibody is described (p. 6 l. 25-27). Antibody fragments and hybridoma cells producing the antibody are disclosed (p. 20 l. 1-8 and p. 20 l. 9 - p. 25 l. 26). HT29 and Caco2 cells appear to express DR5 on their surface (see documents D2 and D3). Therefore, the subject-matter of claims 1-6,13, 14, 17-20, 26-32, 36-39, 44-47, 52 and 53 is not considered novel in the sense of Article 33(2) PCT.

V.2.2 With respect to claims 12-16, 21, 22, 26, 52 and 53

Document D4 describes human antibodies against TGFbeta (p. 1 l. 8-11). The nucleic acid sequence (SEQ ID NO.: 7) encoding for the produced antibody comprises a nucleic acid sequence which is 100% identical to the nucleic acid sequence of the VH region present in the present application. Furthermore, functional fragments of said antibody are described (p. 17 l. 25 - p. 18 l. 21). Furthermore, a pharmaceutical composition and a diagnostic kit comprising said antibody are described (p. 38 l. 6-20). Therefore, the subject-matter of claims 12-16, 21, 22, 26, 52, and 53 is not considered novel in the sense of Article 33(2) PCT.

V.2.3 With respect to claims 23 and 26

Document D5 describes a monoclonal antibody produced by a hybridoma cell line comprising the amino acid sequence which shows 98.148% identity to the VL region as referred to SEQ ID NO. 3 of the present application (see SEQ ID NO. 73 of D5). Therefore, the subject-matter of claims 23 and 26 is not considered novel in the sense of Article 33(2) PCT.

V.2.4 With respect to claims 3, 6, 12-14, 16, 29-33, 36-41, 44-49, 52, and 53

Document D6 describes human or monoclonal antibodies and fragments derived

therefrom against erbB2 which induce cell death via apoptosis (p.9 l. 23-30, p. 14 l. 26-34). Furthermore, said antibodies are used to treat humans suffering from, among others, ovarian cancer (p. 10 l. 38-44) and to detect a tumor using a diagnostic kit comprising said antibody (p. 5 l. 5-7 and p. 24 l. 46-55). Immunoconjugates conjugated to a toxin being an enzymatically active toxin or to radionuclides are disclosed (p. 17 l. 15-24). Therefore, the subject-matter of claims 3, 6, 12-14, 16, 29-33, 36-41, 44-49, 52, and 53 is not considered novel in the sense of Article 33(2) PCT.

Thus, claims 1-6, 12-23, 26-33, 36-41, 44-49, 52, and 53 are not considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 34, 35, 42, 43, 50 and 51

The subject-matter of claims 34, 35, 42, 43, 50, and 51 is considered novel in the sense of Article 33(2) PCT. However, said subject-matter is considered to fall under the routine practice of a person skilled in the art. Therefore, said claims are not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claims 7-11, 24, and 25

A polypeptide as defined in claims 7-11 or a cell producing said polypeptide as defined in claims 24 and 25 is not disclosed or suggested in the available prior art documents. Therefore, the subject-matter of claims 7-11, 24, and 25 is considered novel and inventive in the sense of Articles 33(2) and (3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-35, 52 and 53

The subject-matter of claims 1-35, 52 and 53 appears to be susceptible of industrial application.

V.4.2 With respect to claims 36-51

The subject-matter of claims 36-51 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 36-51 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 Remark concerning documents D7 and D8

Documents D7 and D8 are published in March 2002 and in the year 2002, respectively. Since the Applicants contributed to these publication, they are invited to provide the exact publication date of said articles. The examination report has been based on an assumed valid priority for the present application. In any case, should the priority of the present application not be valid, the above cited documents would be relevant with respect to novelty and inventive step (Article 33(2) PCT).

Further remarks

1. **With respect to claims 7, 8, 15, 21, and 23**

The term "substantially identical" used in claims 7, 8, 15, 21, and 23 is vague and open to interpretation and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Furthermore, the subject-matter of claims 21 and 23 appears to be broader than justified by the application as originally filed, since polypeptides comprising a sequence that is "substantially identical" to the SEQ ID NO. 1 or 3, i.e. at least 75%, 80%, 85% or 90% identity as defined on p. 13 of the present application, rarely show the functional feature of inducing apoptosis. Therefore, claims 21 and 23 do not meet the requirements of Article 6 PCT.

2. **With respect to claim 16**

The phrase "comprising a fragment of the sequence of SEQ ID NO:1 or SEQ ID NO:3" encompasses each and every single amino acid comprised within said sequences. Therefore, claim 16 does not appear to be meaningful.

3. **With respect to claims 36-51**

The subject-matter of claims 36-51 does not meet the requirements of Article 6 PCT in that said claims disclose a method of treatment "comprising the step of contacting a cell or tissue sample with the purified polypeptide", which is considered to be performed ex vivo. It is unclear how the patient should be treated successfully by only performing the before-mentioned step.

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